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Title: Individually Addressable Micro-Electromagnetic Unit Array Chips, Electromagnetic Biochips and Their Applications

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ABSTRACT

This invention provides individually addressable micro-electromagnetic unit array chips and electromagnetic biochips, as well as methods of utilizing these chips for directed manipulating micro-particles and micro-structures such as biomolecules and chemical reagents. An electromagnetic biochip comprises an individually addressable micro-electromagnetic unit array chip and ligand molecules on its surface. By controlling the on/off status of electromagnetic field at each unit of the array and combining this control with magnetic modification of biomolecules, these chips can be used for directed manipulation and release of biomolecules in order to increase sensitivity of bio/chemical analysis and reduce assay time. Other advantages with these chips include minimized damages to biological molecules and increased reproducibility of assay results.

CLAIMS

1. An individually addressable micro -electromagnetic unit array chip comprising:
   a substrate (1);
   an array of hollow (4) on the substrate (1);
   an iron-core (7) in each hollow (4);
   a first layer of conductive wires (2), that lie between every columns of the iron-cores, on the substrate (1);
   a first insulation layer (3) that covers the first layer of conductive wires (2);
   a second layer of conductive wires (9) on the surface of first insulation layer (3), which lie between every rows of the iron-cores and are perpendicular to the direction of the first layer conductive wires (2); and
   a second insulation layer (11) that covers both the iron-cores (7) and the second layer of conductive wires (9).

2. The micro -electromagnetic unit array chip of claim 1, wherein top surface of the iron-cores (7) is between top surface of the first insulation layer (3) and top surface of the second layer of conductive wires (9).

3. The micro-electromagnetic unit array chip of claim 1 and 2, wherein cross section of the hollow (4) is an inverse trapezoid, and an insulation layer is deposited on its side wall (5).

4. The micro -electromagnetic unit array chip of claim 3, wherein a third insulation layer (8) between the first insulation layer (3) and the second layer of conductive wires (9) covers the iron-cores array (7).

5. The micro -electromagnetic unit array chip of claim 1, further comprising single or multiple two dimensional conductive wire network above the insulation layer (11). The network consists of two layers of conductive wires that are insulated from each other and whose position coincides with the first layer conductive wire (2) and second layer conductive wire (9), respectively.

6. The micro -electromagnetic unit array chip of claim 1, wherein the first layer of conductive wires (2) and the second layer of conductive wires (9) are powered by a DC current source.

7. The micro -electromagnetic unit array chip of claim 1, wherein material of the substrate (1) may be any one among silicon, glass, silicon dioxide, plastics or ceramics. The substrate (1) may be either solid or porous materials.

8. The micro -electromagnetic unit array chip of claim 1, wherein the first layer conductive wires (2) and the second layer conductive wires (9) may use any one of the following materials: aluminum, gold, silver, tin, copper, platinum, palladium, carbon, semiconductor materials, or composite of above materials.

9. The micro -electromagnetic unit array chip of claim 1, wherein materials of the first insulation layer (3) and the second insulation layer (11) may be any one among silicon dioxide, plastics, glass, photoresist, rubber, or ceramics.

10. The micro-electromagnetic unit array chip of claim 4, wherein materials of the first insulation layer (3), the second insulation layer (11), the third insulation layer (8), and the insulation layer (5) may be any one among silicon dioxide, silicon nitride, plastics, glass, photoresist, rubber, or ceramics.

11. An individually addressable electromagnetic biochip apparatus comprising an individually addressable micro-electromagnetic unit array chip and comprising
    a substrate (1);
    an array of hollow (4) on the substrate (1);
    an iron-core (7) in each hollow (4);
    a first layer of conductive wires (2) on the substrate (1), which lie between every column of the array;
    a first insulation layer (3) that covers the first layer of conductive wires (2);
    a second layer of conductive wires (9), that lie between every rows of the iron-cores and are perpendicular to direction of the first layer conductive wires (2), on the surface of first insulation layer (3); and
    a second insulation layer (11) that covers both the iron-cores (7) and the second layer of conductive wires (9).
    The electromagnetic biochip further including,
    a thin layer (12) above surface of the individually addressable micro-electromagnetic unit array chip, which is used to bind ligand molecules (13); and
    ligand molecules (13) that are directed and immobilized into the thin layer (12) using magnetic manipulation.

12. The electromagnetic biochip of claim 11, wherein top surface of the iron-cores (7) is between top surface of the first insulation layer (3) and top surface of the second layer of conductive wires (9).

13. The electromagnetic biochip of claim 11 and 12, wherein cross section of the hollow (4) is an inverse trapezoid, so that an insulation layer may be deposited on the side wall (5).

14. The electromagnetic biochip of claim 13, wherein a third insulation layer (8) between the first insulation layer (3) and the second layer of conducting wire (9) covers the iron-cores array (7).

15. The electromagnetic biochip of claim 11, further comprising single or multiple two dimensional conductive wire network between the insulation layer (11) and the thin layer (12) for binding ligand molecules. The network consists of two layers of conductive wires that are insulated from each other and whose position coincides with the first layer conductive wires (2) and the second layer conductive wires (9), respectively.

16. The electromagnetic biochip of claim 11, wherein the first layer of conductive wires (2) and the second layer of conductive wires (9) are powered by a DC current source.

17. The electromagnetic biochip of claim 11, wherein material of the substrate (1) may be any one among silicon, glass, silicon dioxide, plastics or ceramics. The substrate (1) may be either solid or porous materials.

18. The electromagnetic biochip of claim 11, wherein the first layer conductive wires (2) and the second layer conductive wires (9) may use any one of the following materials: aluminum, gold, silver, tin, copper, platinum, palladium, carbon, semiconductor materials, or composite of above materials.

19. The electromagnetic biochip of claim 11, wherein materials of the first insulation layer (3) and the second insulation layer (11) may be any one among silicon dioxide, plastics, glass, photoresist, rubber, or ceramics.

20. The electromagnetic biochip of claim 14, wherein materials of the first insulation layer (3), the second insulation layer (11), the third insulation layer (8), and the insulation layer

(5) may be any one among silicon dioxide, silicon nitride, plastics, glass, photoresist, rubber, or ceramics.

21. The electromagnetic biochip of claim 11, wherein the thin layer (12) for immobilizing ligand molecules is formed by either chemical modification of the insulation layer or coating a polymer layer on top surface of the micro-electromagnetic unit array chip.

22. The electromagnetic biochip of claim 11, wherein the thin layer (12) for immobilizing ligand molecules is made of either functionalized hydrophilic single molecule membrane, functionalized hydrophilic gel, polymer film, porous materials, or a layer of composite of these materials.

23. The electromagnetic biochip system of claim 11, further comprising a fluidic chamber for containing solutions and two channels connected to the chamber for introduction and withdrawal of liquids.

24. A method for directed manipulation of molecules, comprising these steps:
    a. constructing an individually addressable micro-electromagnetic unit array chip as said in claim 1;
    b. forming a thin layer for immobilizing ligand molecules on surface of the above chip;
    c. magnetic modification or load of the ligand molecules;
    d. positioning and immobilizing magnetically-modified ligand molecules on the designated microlocations to form molecule-binding regions on the chip surface by selectively controlling electrical current in the conductive wires in the micro-electromagnetic unit array chip to produce magnetic fields around the designated micro-electromagnetic unit;
    e. magnetic modification of target molecules, in order to link them with magnetic micro-beads;
    f. introducing solution containing target molecules that already linked with magnetic micro-beads onto the micro-electromagnetic unit array chip that already bound with specific ligand molecules;
    g. alternatively addressing every unit on the micro-electromagnetic unit array chip to produce magnetic field at designated units, thereby the target molecules with magnetic modification can be directed to approach the affinity binding ligand

molecules on the designated units of the chip so as to accomplish affinity binding reaction; and

h. separating target molecules and magnetic micro-beads, and removing the magnetic micro-beads.

25. The method of claim 24, wherein the thin layer for immobilizing ligand molecules is formed by either chemical modification of the insulation layer or coating a polymer layer on top surface of the micro-electromagnetic unit array chip.

26. The method of claim 24, wherein the thin layer for immobilizing ligand molecules is made of either functional hydrophilic single molecule membrane, functional hydrophilic gel, polymer film, porous materials, or a layer of those composites.

27. The method of claim 24, wherein the magnetic modification of ligand molecules is to link ligands with magnetic micro-beads by a cleavable linker.

28. The method of claim 27, wherein the link of ligands with magnetic micro-beads is due to covalent bond or biological affinity between the functional group of the cleavable linker and functional group of the magnetic micro-beads.

29. The method of claim 27, wherein the cleavable linker is either photo-cleavable linker, thermal cleavable linker, enzymatic cleavable linker, or other chemical cleavable linker.

30. The method of claim 24, wherein the magnetic modification of ligand is to mix solution of ligand and magnetic micro-beads and freeze a drop at high cooling rate to form small solid particles containing a mixture of magnetic micro-beads and biological samples. The solid particles may be transported by three-dimensional precision robotic arms and a specially-designed magnetic micro-particle dispenser.

31. The method of claim 24, wherein for the affinity binding site on the surface of each micro-electromagnetic unit, the vertical dimension is between one nanometer (1nm) and one thousand micrometer (1000μm), and the horizontal dimension is between half micrometer (0.5μm) and five millimeter (5mm).

32. The method of claim 24, wherein the magnetic modification of target molecules is to link target molecules (*** INSTEAD OF LIGAND ***) with magnetic micro-beads by a cleavable linker.

33. The method of claim 32, wherein the link of target molecules with magnetic micro-beads is due to covalent bond or biological affinity between the functional group of the cleavable linker and functional group of the magnetic micro-beads.

34. The method of claim 32, wherein the cleavable linker may be either photo-cleavable linker, thermal cleavable linker, enzymatic cleavable linker, or other chemical cleavable linker.

35. The method of claim 24, wherein the method of separating ligand or target molecules from magnetic micro-beads is to apply optical, enzymatic, or chemical cleavage method, in order to break the cleavable linker.

36. The method of claim 35, wherein the separation of target molecules and magnetic micro-beads at the cleavable linker is performed by illumination of 250nm to 750nm light, or by urease cleavage.

37. The method of claim 24, wherein the magnetic micro-beads are removed either by applying a magnetic field on top of the chip or by fluidic wash.

38. The method of claim 24, wherein the magnetic field or electric current is gradually increased or decreased.

39. The method of claim 24, wherein multiple, different target molecules are simultaneously controlled by electromagnetic field, transported and concentrated onto the affinity binding site of the micro-electromagnetic unit array chip.

40. The method of claim 24 to 39, wherein said ligands and target molecules may be either biomolecules, chemical reagens, or drug molecules.

41. The method of claim 24 to 39, wherein said ligand is a DNA probe with specific sequence and target molecules are DNA molecules.

42. The method of claim 24 to 39, wherein said ligand is an antibody and target molecules are antigen in the testing samples.

DESCRIPTIONS

Individually addressable micro-electromagnetic unit array chips, electromagnetic biochips and their applications

The present invention discloses novel, individually addressable micro-electromagnetic unit array chips and electromagnetic biochips. Using these apparatus according to the present invention, by controlling the on/off status and the magnitude of electromagnetic fields at microlocations on chip surfaces, it is possible to manipulate magnetically-modified biomolecules and bioparticles such as DNA, proteins, cells and to connect paramagnetic micro particles or microstructures for performing minaturized, high-speed and high-throughput bio/chemical assay and clinical diagnosis. In addition, the present invention discloses methods of utilizing the electromagnetic biochips for manipulating biomolecules, bioparticles, chemical reagents and microstructures, as well as methods of control procedures and detection approaches for bio/chemical assays.

As a novel and emerging technology in life science and biomedical research during last several years, biochip technology can be applied to many areas of biology, biotechnology and biomedicine including point-mutation detection, DNA sequencing, DNA expression, drug screening and clinical diagnosis. Biochips are produced using microelectronic and microfabrication techniques in semiconductor industry or other similar techniques, and can be used to integrate and shrink the currently discrete bio/chemical analytical processes and devices into microchip-based apparatus. There are two kinds of biochips, i.e., passive and active. Passive biochips refer to those on which bio/chemical reactions are dependent on passive diffusion of sample molecules. Majority of the available biochips belongs to passive type. For example, The light-directed chemical synthesis process developed by Affymetrix is a method of synthesizing biomolecules on chip surfaces by combining solid-phase photochemical synthesis with photolithographic fabrication techniques. The chemical deposition approach developed by Incyte Pharmaceutical uses pre-synthesized single-nucleotide cDNA probe for directed deposition onto chip surfaces. The contact-print method developed by Stanford University uses high-speed, high-precision robot-arms to move and control liquid-dispense head for directed cDNA deposition and printing onto chip surfaces. The University of Washington at Seattle developed a single-nucleotide probe synthesis method by using four piezoelectric deposition heads, which are loaded separately with four types of nucleotide molecules to achieve required deposition of nucleotides and simultaneous synthesis on chip surfaces. Although these types of biochip, just like active biochips, are also made of arrays having different ligands, their fabrication did not make full use of various

techniques and methods employed in microfabrication and microelectronic technologies. Although passive biochips can have a significant impact on life science and biomedical research, they cannot be readily used to achieve fully integration and miniaturization of the entire bio-analytical system from the front-end sample preparation to final molecular quantification/detection, and to reduce costs and to improve throughput. In addition, passive biochips have other disadvantages including low analytical sensitivity, a long reaction time that is necessary for complete biomolecule reactions, and difficulties associated with control of temperature, pressure, electrical/magnetic field at individual site (or called unit) on chip surfaces.

Certain types of active biochips produced with various microfabrication techniques allow for versatile functions such as microfluidic manipulation, PCR and capillary electrophoresis, however, they cannot be readily used for high throughput applications. The electronic biochips developed by Nanogen can manipulate and control bio-sample molecules with electrical field generated by microelectrodes, leading to significant improvement in reaction speed and detection sensitivity over passive biochips. However, there are four shortcomings of Nanogen biochips.

(1) When microelectrodes are energized with electrical potential/currents, local pH values near electrode surfaces are altered because of electrochemical reactions, leading to possible damages to sample molecules.

(2) To effectively move biomolecules in their suspension/solutions with electrical fields, electrical conductivity of solutions has to be very low. This significantly limits the choice of buffer solutions used for bio/chemical assays.

(3) The complicated electrochemistry on microelectrode surfaces results in a poor reproducibility of system performance.

(4) Nanogen biochips exploit the electrical charges possessed by sample molecules in solutions and transport molecules with electrical forces to reaction sites. This method can direct (or transport) large biomolecules such as DNA and proteins to reaction sites effectively and quickly. A major limitation is that it can be used to transport only relatively-homogeneous large biomolecules, i.e. the molecules that have same polarity of charges when suspended or dissolved in certain buffer solutions. Because of the differences in isoelectric points of molecules, different biomolecules such as DNA and proteins in a particular buffer solution may possess different magnitude and polarity of electrical charges. Thus, it cannot be used simultaneously transport biomolecules having electrical charges of different polarities in the same direction.

The present invention discloses individually addressable micro-electromagnetic unit array chips. Such chips can be used to magnetically manipulate biomolecules and chemical molecules.

The present invention overcomes shortcomings of current biochips by utilizing novel individually addressable electromagnetic biochips. Such chips comprise individually addressable micro-electromagnetic unit array chips. By controlling the on/off status and magnitude of electromagnetic fields at individual unit in the array and combining such control with the magnetic modification of biomolecules/bioparticles, the electromagnetic biochips can accomplish directed manipulation and release of biomolecules/bioparticles so as to increase the sensitivity of bio/chemical assays and to reduce assay time. Other advantages of bio/chemical assays using the electromagentic biochips are that biomolecules are not damaged, a variety of biomolecule suspension/solution buffers can be used, and the assay processes and results are reproducible.

The present invention further discloses methods for manipulating biomolecules/ bioparticles, chemical-reagent molecules or drug molecules.

According to one embodiment of the present invention, an individual addressable micro-electromagnetic unit array chip comprises

a substrate;

an array of hollow on the substrate;

an iron-core in each hollow;

a first layer of conductive wires on the substrate that lie between every columns of iron-cores;

a first insulation layer on the substrate surface that covers the first layer of conductive wires;

a second layer of conductive wires on the surface of the first insulation layer that lie between every rows of iron-cores and are perpendicular to direction of the first conductive wires;

a second insulation layer on the chip surface that covers the iron-core array and the second layer of conductive wires.

In one embodiment of the present invention, an electromagnetic biochip comprises an individually addressable micro-electromagnetic unit array chip that comprises

a substrate:

an array of hollow on the substrate;
an iron-core in each hollow;
a first layer of conductive wires on the substrate that lie between every columns of iron-cores;
a first insulation layer on the substrate surface that covers the first layer of conductive wires;
a second layer of conductive wires on the surface of the first insulation layer that lie between every rows of iron-cores and are perpendicular to direction of the first layer conductive wires;
a second insulation layer on the chip surface that covers the iron-core array and the second layer of conductive wires;
a thin layer that covers the second insulation layer and is used to immobilize ligand molecules; and
ligand molecules that are directed and immobilized into the thin layer by magnetic manipulation.

According to one embodiment of the present invention, a method for manipulating biomolecules, chemical reagents, or drug molecules comprises these steps:

a. constructing the above-mentioned individually addressable micro-electromagnetic unit array chips;
b. forming a thin layer for immobilizing ligand molecules on the chip surfaces;
c. magnetic modification or load of the ligand molecules;
d. positioning and immobilizing magnetically-modified ligand molecules on the desired microlocations to form molecule-binding regions on the chip surface by selectively controlling electrical current in the conductive wires in the micro-electromagnetic unit array chip to produce magnetic fields around the desired micro-electromagnetic unit;
e. magnetic modification or load of target molecules to link them with magnetic beads;
f. introducing solutions containing magnetic-bead-linked target molecules onto the above-described ligands-containing micro-electromagnetic unit array chip;
g. producing magnetic fields around desired micro-location by selectively addressing and energizing the unit within mciroelectromagnetc unit array so that magnetically modified target molecules can be directed to approach ligand molecules on the desired unit location so as to accomplish binding reaction;
h. separating magnetic beads from target molecules; and removing magnetic beads.

The ligands and target molecules in the above method may be biological molecules, chemical reagents, or drug molecules.

Methods according to the present invention may be used for hybridization and detection for specific sequences of DNA molecules, for antibody/antigen binding interaction in application areas such as drug screening, bio/chemical process control, biochemical monitoring and clinical diagnosis.

In the following, with the aid of figures, we provide detailed descriptions of exemplary embodiments of individually addressable electromagnetic array chips, electromagnetic biochips, and methods of manipulating molecules.

Figure 1a is a schematic diagram showing the structures of an individually addressable microelectromagnetic unit array chip.

Figure 1b is a schematic diagram showing the electrical current flow for turning on a microelectromagnetic unit.

Figure 2 is a schematic diagram showing an individually addressable electromagnetic biochip.

Figure 3 is a schematic representation showing magnetic modification of ligand or target molecules through cleavable linker.

Figure 4a – 4I is a schematic representation of the method for manipulating molecules according to the present invention.

Figure 1a is a schematic representation of structures for an exemplary embodiment of individually addressable microelectromagnetic unit arrays, in which one microelectromagnetic unit is shown with details.

The micro-electromagnetic unit array chip comprises a single-side polished silicon substrate (1) that has phosphorus-doping leading to an electrical resistivity of 2 – 10 □cm. Using thermal growth method, the substrate surface may form a layer of SiO_2 having a thickness between, for example, 1000 and 8000 Å (angstrom).

Based on the requirement of dimensions and array density for the micro-electromagnetic unit array chip, the parallel conductive wires (2) can be photolithographically formed on the substrate (1) by phosphorus injection. The surface density of phosphorus diffusion should give the sheet-resistance less than or equal 10 □/square.

After forming the first layer of conductive wires (2), a SiO_2 layer with a thickness of 2000-4000 Å may be grown on the surface of the substrate (1) by placing the chip into a high temperature oven (1000°C), so that the first insulation layer of SiO_2 (3) on the substrate (1) is formed to cover the first layer of conductive wires (2).

Using photolithography method, hollows for electroplating are created on the designated areas between the first layer conductive wires (2). For example, an array of 10 μm deep electroplating hollows (4) is etched by applying a 30% of KOH solution on the silicon substrate. The cross section of the electroplating hollows should be a shape of inverse trapezoid.

A SiO_2 layer (5) with thickness of 5000 Å is deposited on the surface of the electroplating hollows (4), and the SiO_2 layer at the bottom of electroplating hollows (4) is removed by photoetching.

The substrate (1) is placed into a $NiSO_4$ solution (200-400g/l) and heated upto 400-600°C for 30 minutes under nitrogen gas, so that a seed layer with thickness such as 1 μm is formed at the bottom of the electroplating hollows (4).

Furthermore, using following the steps and conditions, an iron-core (7) for each hollow may be electroplated: (1). in Fe: $FeCl_2$ solution (ratio 200:500 g/l) at 20-40 °C; (2). in FeNi:$NiSO_4$ solution (200:400 g/l) at 30-60 °C; (3). in $FeCl_2$ solution (10-60 g/l) at 30-60 °C. An iron-cores array is formed on the substrate (1), while the top surface of the iron-cores (7) is higher than the top surface of the SiO_2 insulation layer (3).

After electroplating, a Si_3N_4 insulation layer (8) with thickness such as 5000 Å is deposited on the surface of substrate (1) at 200-300 °C.

Then, a layer of Aluminum with thickness such as 1.2μm is sputtered onto the surface of Si_3N_4 (8) insulation layer. A second layer conductive wires (9), that are perpendicular to

direction of the first layer electronic wires (2), is formed between the iron-cores (7) by photolithography and wet etching methods. Therefore, a micro-electromagnetic unit array that consists of the iron-cores array and two dimensional network of conductive wires is formed on the substrate (1). The top surface of second layer of aluminum conductive wires (9) is higher than the top surface of iron-cores (7).

A Si_3N_4 insulation layer (11) with thickness such as 4000 Å is deposited on surface of the aluminum cnductive wires (9) at 300 °C.

Then, the insulating materials on ends of the first layer conductive wires (2) and the second layer conductive wires (9) are removed by dry etching method, so that the ends of conductive wires are exposed in order to connect with the external electric circuits.

The conductive wires (2) and (9) on the micro-electromagnetic unit array are powered by a DC current source. The individual unit on the micro-electromagnetic unit array is controlled by selectively controlling electric current in different wires. As shown in figure 1b for details, the magnetic field is produced around the selected iron-core unit by choosing the direction of electric current through the wires nearby to form a closed circuit loop around the iron-core unit.

To increase the intensity of magnetic field, single or multiple two dimensional conductive wires network may be added on the top of insulation layer (11) by similar method that creating the conductive wires (2) and (9). The network consists of two layers of conductive wires that are insulated from each other and whose position coincides with the conductive wires (2) and (9), respectively.

In this example, the material for the substrate is silicon, but other materials, such as glass, silicon dixoide, plastics and ceramics etc., may also be used. The substrate can use either solid or porous materials. Similarly, the materials for the insulation layer (3), (5), (8), (11) are not limited to the one used in this example, but may be plastics, glass, photoresist, rubber, ceramics etc. The conductive wires may be aluminum, gold, tin, copper, platinum, palladium, carbon, semiconductor materials or composite of above materials. A micro-electromagnetic unit array chip in the present invention may be made by above-described methods. Using such chips, directed manipulation of biomolecules, chemical reagents and drug molecules is made possible through the application of magnetic fields.

After the micro-electromagnetic array chips are fabricated, the surface of insulation layer (11) may be chemically modified or may be coated by a layer of polymer film. This layer is called functional layer (12), which is used for immobilizing ligand molecules. As described in figure 2, the functional layer (12) may be functional hydrophilic monomolecule membrane, functional hydrophilic gel, polymer layer, porous materials and the composite of these materials.

After the formation of functional layer, the ligand molecules (13) that have been magnetically modified or loaded may be immobilized into the thin-layer by magnetic field.

In order to hold the affinity ligands, reagents and reactants, and to allow the liquids flowing in and out of the reaction center, a fluid chamber needs to be constructed on the chips, which allows for the liquid transportation and optical detection.

Thus, we have completed the description of the construction of one example of individually addressable micro-electromagnetic biochips according to the present invention.

Figures 3 and 4 illustrate methods for constructing electromagnetic biochips and methods of manipulating biomolecules, chemical molecules and drug molecules according to the present invention. These methods include following steps:

a. Constructing an individually addressable micro-electromagnetic array chip.
b. Constructing a functional layer (12) on the surface of the above chip. This functional layer is used for immobilizing ligand molecules.

The layer may be formed by direct chemical modification of the surface of the insulation layer or by polymer coating (figure 2). The layer may be a functional hydrophilic monomolecular membrane, functional hydrophilic gel, polymer layer, porous layer or the composite of these materials.

c. magnetic modification or load of the ligand molecules that will immobilized.
d. By controlling electric current in individual wires, magnetic field at desired micro-electromagnetic units is turned on so that the magnetically modified or loaded ligand molecules may be manipulated and immobilized at desired microlocations into the above-described functional layer. This will form affinity binding regions on the chip surfaces.

There are several methods to manipulate and immobilize the ligand molecules onto specific regions by magnetic field application. For example, the ligand (13) may be linked onto a paramagnetic bead (15) through a cleavable linker (14). Thus, this ligand can be transported, manipulated and released to specific regions by applying magnetic field.

The cleavable linkers can be photocleavable, heat cleavable, enzyme cleavable or other chemical cleavable.

The connection of a cleavable linker and a paramagnetic micro-bead may be realized by the chemical reaction or bioaffinity between the end functional group (16) of the cleavable linker and the functional group (17) of paramagnetic micro-bead. For example, the connection can be obtained by:

Ligand--cleavable linker—biotin—streptavidin--paramagnetic microbead

Another method for magnetically loading ligands is to mix the solution containing ligand with paramagnetic micro-beads and then rapidly frozen them to form solid micro-particles (18) containing the ligands and the paramagnetic micro-beads. The solidified micro-particles prepared from different samples may be stored at a freezer for future applications. Directed transportation of such solidified micro-particles on the chip may be achieved by three-dimensional precision robotic arms and a specially designed magnetic micro-particle dispenser (19). When the solidified micro-particles are carried to the positions above the designated region on the chip, the micro-particles may be released and immobilized (figure 4a) on spot by controlling the electric current at the designated micro-electromagnetic unit so that the magnetic field on the chip region is stronger than the field on dispenser head. Thus, the solidified micro-particles are released onto the functional layer of the chip at the designated regions (figure 4b). After liquefying the solid micro-particles, the ligand molecules are immobilized on the designated chip regions (figure 4c). Such steps have additional advantages that the cross contamination between ligand molecules by the magnetic dispenser is reduced to minimum without cleaning the dispenser head after each delivery. After the immobilization of ligand molecules on the chip surfaces is complete, the magnetic microbeads may be removed from the chip by additional magnetic forces above the chip surface or by fluidic wash (figure 4d).

The affinity binding area on each micro-electromagnetic unit on the chip is between 1 nm-1000μm(long) and 0.5μm-5mm(wide).

e. Target molecules (20) is modified and connected onto the magnetic microbeads (15).

In order to use the individually addressable micro-electromagnetic chips described in this invention to manipulate the target molecules, these molecules need first to be magnetically modified.

There are several methods to magnetically modify the target molecules. For example, the target molecules may be linked onto a paramagnetic bead (15) through a cleavable linker (14) so that the target molecules may be manipulated and relaesed on-spot by applying magnetic fields.

Cleavable linkers can be photocleavable, heat cleavable, enzyme cleavable or other chemical cleavable.

The connection of cleavable linker and a paramagnetic microbead may be realized by the chemical reaction or bioaffinity between the end functional group (16) of the cleavable linker and the functional group (17) of paramagnetic microbead. For example, the connection may be obtained by (figure 4e):

Target molecules--cleavable linker—biotin—streptavidin--cis magnetic microbead

f. The target molecules that have been linked to magnetic beads placed in the fluidic chamber are made in contact with the ligand molecules immobilized on biochip surfaces.

g. By alternative connecting and disconnecting the individual wires on the biochips (figure 4f and 4g), the magnetic field generated at individual micro-electromagnetic units attracts the magnetically-modified target molecules and moves them close to the designated ligand affinity binding regions. Therefore the affinity binding reaction between target molecules and the ligand molecules is promoted (figure 4h).

When the magnetically-modified target molecules are introduced onto the electromagnetic biochips for analyses, the motion of the target molecules is random (figure 4e). The directed movement of the sample molecules to all the micro-electromagnetic units is achieved by applying magnetic fields through alternatively connecting and disconnecting the electrical wires as illustrated in figure 4f an d4g. Under the influence of the magnetic field generated by the selectively-addressed micro-electromagnetic unit , the magnetically-modified target molecules can be caused to

rapidly approach the biochip surface, and to undergo the affinity binding reactions with the ligand molecules immobilized in the designated unit regions.

h. Separate the target molecules from the magnetic microbeads and remove the microbeads. Separation of target molecules from magnetic microbeads can be realized by photocleavage, enzymatic digestion, chemical cleavage of the cleavable linker between target molecule and microbeads (41). The magnetic microbeads can be removed from the chip by additional magnetic forces above the chip surface or by liquid flow cleaning.

In above-mentioned method, the ligands and target molecules can be biological, chemical or pharmaceutical.

The methods in this invention can be applied for determination of specific DNA sequences by hybridization, binding assays of antigen-antibody reactions and drug screening. Therefore, this invention can be applied to perform controlled biochemical reactions, biochemical detection and clinical diagnostic detection.

When the above-described methods are used for DNA hybridization, after step h, non-specific hybridized DNA molecules are removed by stringent control of the binding conditions, such as hybridization buffer, temperature etc., and whereas the specific hybridized DNA molecules remain on the affinity binding area.

When the above-described methods are used for antigen-antibody interaction, after step h, non-specific bound antigen or antibody molecules are removed by stringent buffer washing conditions and whereas the specific bound antigen or antibody molecules remain on the affinity binding area.

When the above-described methods are used for biological analyses, the detection and quantification of the analytical results may be obtained using several detection methods, such as optical signals, magnetic-electric conversion signals, etc. Optical detection can be realized by detecting the florescence signals carried by the target molecules, which is excited by laser light source. This method is rapid , highly sensitive (figure 4j). Another optical detection method utilizes florescence tagged probes or secondary antibody which specifically bind to the target molecules, and then the florescence are induced by laser light source.

The following is a practical example for controlled DNA molecule operation that uses the methods of this invention.

First, an individually addressable micro-electromagnetic array chip is constructed according to the methods described in this invention. The surface of the chip is coated with a layer of high molecular polymer for DNA probe immobilization.

The paramagnetic microbeads are added into the solution containing DNA probes and quickly frozen to form solid microbeads. The microbeads are transported onto the top of the designated regions (micro-electromagnetic units) of the biochip through the precision robot and magnetic dispenser. The stronger magnetic field is generated on the unit of the biochip by connecting electronic circuit around the selected region. The probe mixed microbeads is released on the functional layer of the specific units on the biochip. When the microbeads are defrosted, DNA probes in the liquid is immobilized on the designated unit (region) on the biochip. Then the free magnetic microbeads are removed by an additional magnetic field applied above the surface of the biochip. Thus an affinity binding region is formed.

The target DNA molecules are linked to the one end of a photocleavable linker. On the other end of the linker there is a biotin tag. Streptavidin is immobilized on the surface of the magnetic microbeads. Then, they are mixed together. The target DNA molecules are linked to magnetic microbeads by biotin-streptavidin interaction.

DNA target-photocleavable linker-biotin—streptavidin-magnetic microbeads.

Place the solution containing magnetically-modified target DNA molecules into the liquid chamber on the biochip. Alternatively turn on and turn off the micro-electromagnetic unit to produce magnetic fields in each unit on the chip. The target DNA molecules that are modified with magnetic microbeads are moved to the probe DNA molecules that have been immobilized on the chip surfaces. The target DNA molecules, therefore, are hybridized to the probe molecules on the affinity binding regions under the pre-selected hybridization conditions.

The magnetic microbeads are separated from target DNA molecules by irradiation with 250nm-750nm light. The light irradiation cleaves the photocleavable linker to disconnect DNA and magnetic beads. The free magnetic beads are removed from reaction regions on the chip by additional magnetic forces.

The above-described example is believed to be a better approach for utilizing this invention by inventors. However, the described parameters such as methods, protocols, measurements, temperatures, concentrations and time should not be considered to be the limits of this invention.